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ORIGINAL PAPER

Improved microcirculation in patients with an acute ST-elevation myocardial infarction treated with the Impella LP2.5 percutaneous left ventricular assist device

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Abstract
Background Circulatory support during percutaneous coronary intervention (PCI) in patients with ST-element elevation myocardial infarction (STEMI) aims at maintaining hemodynamic stability and organ perfusion. However, continuous flow pumps may interfere with the normal pulsatile circulation and the microcirculatory function. Sidestream dark field (SDF) imaging allows the visualization of microvascular structure and function of tissue and may provide information regarding the efficacy of the circulatory support.
Methods Sidestream dark field was used to study the sublingual microcirculation (MC) in six anterior STEMI patients treated with PCI; three patients received Impella LP2.5 percutaneous left ventricular support (Impella group) and three patients received no support (control group). MC was assessed at baseline, at 24, 48 and 72 h after PCI. Data were analyzed using a validated scoring method and the microvascular flow index (MFI) and perfused vessel density (PVD) were calculated. MC of three healthy controls was used as normalized standard.
Results Normal MC depending on both functional capillary density (PVD) and flow velocity or quality (MFI), as observed in healthy controls, was only achieved in the Impella group and paralleled improvement in LV function. Functional capillary density in the control and Impella groups were respectively equal and above the level of healthy controls. The quality of microcirculatory flow only in the Impella group reached values of healthy controls.
Conclusions Microcirculation assessed by SDF improved in STEMI patients treated with the Impella LP2.5 to levels observed in healthy persons and remained suboptimal after 72 h in patients without support. Sublingual SDF to assess MC may serve as a monitor of effective myocardial recovery after PCI and optimization of organ perfusion.

Keywords Myocardial infarction · Angioplasty · Left ventricular assist device · Microcirculation · Impella micro-axial flow pump · Sidestream dark field imaging

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Introduction

Reperfusion therapy for acute ST-elevation myocardial infarction (STEMI) aims at early restoration of coronary circulation [1, 2]. It reduces infarct size and improves residual left ventricular (LV) function after STEMI. Primary percutaneous coronary intervention (PCI) is the choice of treatment for STEMI patients, especially when in cardiogenic shock [3–5]. In STEMI patients with cardiogenic shock, mechanical left ventricular support aims at improving the circulatory conditions of both the coronary arteries and other organs [6–9]. The circulatory response at

microvascular level has been investigated in hemorrhagic and septic shock models, including ischemia–reperfusion injury [10–12]. In patients with heart failure and cardiogenic shock, disturbances of the microcirculation (MC) have also been described. However to date, little is known about the alterations in tissue perfusion and circulatory characteristics at the microvascular level, particularly in the acute phase of STEMI. Additionally, the effect of circulatory support on MC in STEMI patients after PCI has not been studied before [13–16]. Furthermore, the interference of the continuous flow of a circulatory support device with the normal vascular pulsatility is another unsolved issue.

We evaluated the microcirculatory response over time in several conditions with a non-invasive imaging modality called Sidestream dark-field (SDF, Microvision Medical, Amsterdam, The Netherlands) [17–19]. We compared MC between patients treated with and without LV circulatory support by an axial flow pump in STEMI patients after primary PCI. In concordance to the AMC MACH 2 study, we hypothesized that improvement of myocardial function and improved circulation with Impella support would have a positive effect on the peripheral MC and therefore tissue perfusion [20, 21].

Materials and methods

Patients and study design

The study was a sub-study of the non-randomized controlled AMC MACH 2 study and has been approved by the ethics committee of the Academic Medical Center (Amsterdam, the Netherlands) [20, 22]. As described earlier, we hypothesized that mechanical unloading of the left ventricle in STEMI patients treated by PCI may give the myocardium time to recuperate from ischemic stunning and may reduce infarct size. This may be particularly true in STEMI patients with cardiogenic shock or pre-shock, who have a large ischemic area at risk for necrosis. Prior to the initiation of a large trial in this patient category, as prolonged mechanical cardiac support with the novel Impella assist device was never evaluated in the setting of STEMI before, the MACH 2 study was designed to assess safety and feasibility of prolonged Impella support in a group of less severely hemodynamically compromised patients, which still might benefit from left ventricular unloading (i.e. anterior STEMI).

Written informed consent was obtained from each patient prior of inclusion. Patients between 30 and 80 years of age, who presented with a first anterior STEMI within 6 h after onset of symptoms were eligible for enrolment. Exclusion criteria were mainly deep cardiogenic shock, mechanical ventilation, blood transfusion in the previous 24 h, known hemoglobin diseases such as sickle cell or thallasemia, stroke or transient ischemic attack within the previous 4 weeks as well as exclusion criteria related to the ability to insert the Impella device such as: the presence of a mural thrombus in the left ventricle and severe aortic stenosis or the presence of a mechanical aortic valve. The last three consecutive patients with (Impella group $n = 10$) and the last three without circulatory support (non-support control group $n = 10$) of the MACH 2 study were selected for the MC sub-study. The Impella group patients had circulatory support for 3 days with the Impella LP2.5 immediately after primary PCI. The control group received routine care after primary PCI, including IABP therapy, as deemed necessary by the attending operator in one patient. Three healthy controls who matched for age and body mass index provided microcirculatory control data.

Impella LP 2.5

As described earlier, the Impella LP2.5 is a novel catheter (9 Fr) mounted micro-axial rotary blood pump (12 Fr), designed for short-term mechanical circulatory support. It is inserted through a femoral approach and positioned across the aortic valve into the left ventricle. Expelling aspirated blood from the left ventricle into the ascending aorta, the Impella is able to provide flow up to 2.5 L/min.

Data collection and echocardiography

Procedural and laboratory data, clinical history and admission medication were prospectively collected. Blood samples were taken for determination of troponin T, creatine kinase, creatine kinase-MB (CK-MB) and NT-proBNP at admission, post-PCI and every 6 h during the first 72 h of admission.

Global left ventricular ejection function (LVEF) in both groups was determined on transthoracic echocardiography (TTE) immediately after PCI (baseline) and at 3 days (after Impella removal). Baseline TTE also served to assess the presence of LV mural thrombus, which is an exclusion criterion for Impella therapy. A standard imaging protocol was used based on apical 4- and 2-chamber views. Analysis were performed by an independent core lab (DCRI echocardiography core laboratory, Duke University, Durham, NC, USA) blinded to treatment assignment.

Microcirculatory measurements and analysis

Assessment of the sublingual MC was performed using SDF, a hand-held microscope with light-emitting diodes (LEDs) arranged in a ring formation at the tip of the probe. These LEDs emit at a wavelength 550 ± 10 nm which is absorbed by hemoglobin in erythrocytes, which are

visualized as dark flowing cells in the microvascular network consisting of small (0–20 μm), medium (21–50 μm) and large (51 μm and larger) vessels. In the Impella group baseline images of the MC are recorded after PCI but before Impella support. Thereafter, microcirculatory recordings are obtained immediately after start of support, at 24, 48 h of support and after device removal at 72 h. In the non-support control group microcirculatory assessment is performed at corresponding time points. The SDF device is gently placed on the sublingual region of the patients to avoid pressure artifacts. Subsequently, three to five sequences of steady images of various regions were obtained and stored as avi formatted video clips.

Analysis of the microvascular network is carried out by a validated scoring system described by De Backer et al. [23]. For differentiation of the quality or type of flow in the microvascular network the microvascular flow index (MFI) is determined. This score is based on quantification of the predominant type of flow per vessel type (small, medium, large) in four equal quadrants of the obtained image. Flow is characterized as absent (0), intermittent (1), sluggish (2), or normal (3). The MFI score represents the averaged values of the four quadrants [24].

In addition, the perfused vessel density (PVD), which is an estimate of the functional capillary density, is calculated. The PVD is calculated by the percentage of the vessel length of small vessels of all the vessels divided by the analyzed image area. Tissue perfusion or oxygen transport capacity by the MC is dependent on both functional capillary density (reflected by PVD) and blood velocity (reflected by MFI).

Statistical analysis

Data are presented as mean ± SD for continuous variables and as frequencies for categorical variables. Differences between the Impella group and control group in continuous variables were tested with the Student's *t* test. Comparisons between baseline hemodynamic values, baseline LVEF, MFI, PVD, and subsequent measurements were performed in a paired fashion using the Student's *t* test. All tests were two tailed and a P value of <0.05 was considered statistically significant. The statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA; version 15.0) was used for statistical analysis.

Results

Patients

In total six consecutive patients from the MACH2 study were included in this study. Microcirculatory observations of three age and body mass index matched healthy controls were used as normalized standard. All six anterior STEMI patients were treated with primary PCI. After PCI, three patients received Impella support (Impella group) and three patients received routine care (non-support group). The baseline clinical characteristics of the study population are shown in Table 1. Patients of the Impella group had a higher risk profile. At admission the Impella group had higher serum levels of NT-proBNP, CK, CK-MB, peak CK-MB, troponin T, as well as a higher area under the curve of CK-MB and troponin T. In addition, baseline echocardiographic LVEF measurement, revealed a more depressed mean ejection fraction in the Impella group compared to the non-support group (i.e. 28 vs. 45%; $P = 0.06$). In overall, the Impella assisted patients were in worse clinical condition at baseline compared with the control group.

Sublingual microvascular hemodynamics and LVEF

Adequate recordings were obtained at all times for all patients. Figure 1a shows an example of the MC at baseline in a patient from the Impella group. Figure 1b illustrates the MC of the same patient 48 h later during Impella support. In all patients visualization of the MC showed a network of small, medium and large vessels. The MC was assessed for MFI, representing the amount or quality of flow in the microvascular bed, and the PVD, estimating the functional capillary density. The MFI for both groups is depicted in Fig. 2. In the Impella group, the MFI is significantly more impaired at baseline compared to the non-support control group; the MFI scores respectively were 1.8 ± 0.24 and 2.5 ± 0.11 ($P < 0.05$). In other words, the flow of small capillaries is more stagnant in the Impella group at baseline. In the non-support control group no significant changes in MFI are observed during the observation period and the MFI remains below values of healthy controls. In contrast, in the Impella group an immediate improvement of the MFI is observed after initiation Impella support. The MFI increases from 1.8 ± 0.24 at baseline to 1.97 ± 0.27 (P = NS) directly after start of the Impella device, but does not become significant until after 24 h of assisted Impella support. This significant change in MFI from 1.8 ± 0.24 at baseline to 2.5 ± 0.19 ($P < 0.05$) at 24 h of support was sustained even after removal of the Impella at 72 h and remained significantly better than the MFI of non-support controls. With Impella support the quality of flow in the microvascular network did reach the values observed in healthy controls. In contrast to the MFI, the PVD was similar in both groups at baseline (Fig. 3). However whereas the PVD remained equal in the non-support control group, the PVD after 48 h was significantly enhanced in the Impella group, even above values of healthy controls. We found a significant increase of the

Table 1 Baseline characteristics

Variables	Impella $n = 3$	Control $n = 3$	P value
Clinical characteristics and risk factors			
Age (years)	53.6 ± 17.8	57.1 ± 11.7	0.79
Male gender (%)	2 (67)	3 (100)	0.273
Body mass index	25.3 ± 3.4	27.2 ± 6.1	0.665
Family history of cardiovascular disease (%)	1 (34)	1 (34)	
Hypertension (%)	1 (34)	1 (34)	
Diabetes (%)	0	0	
Current smoker (%)	3 (100)	2 (67)	0.273
Hypercholesterolemia (%)	0	0	
Stroke (%)	0	0	
Previous myocardial infarction (%)	0	0	
Previous coronary angioplasty (%)	0	0	
Previous coronary artery bypass grafting (%)	0	0	
Heart rate (bpm)	77.3 ± 22.9	80.3 ± 4.9	0.835
Diastolic pressure (mmHg)	79.0 ± 3.6	70.7 ± 5.0	0.08
Systolic pressure (mmHg)	126.0 ± 16.3	114.7 ± 5.7	0.321
Laboratory			
Serum creatinine (μmol/L)	79.7 ± 27.2	62.7 ± 15.9	0.404
Hemoglobin (mmol/L)	9.2 ± 1.1	9.0 ± 0.5	0.86
Plasma glucose (mmol/L)	7.9 ± 0.6	7.1 ± 0.9	0.67
High sensitivity-CRP (mg/L)	75.6 ± 127.6	1.7 ± 2.2	0.373
NT-proBNP (ng/L)	4151.8 ± 6995.0	154.7 ± 103.2	0.78
CK-MB (μg/L)	105.3 ± 99.0	6.7 ± 5.9	0.16
Peak CK-MB (μg/L)	351.3 ± 124.7	242.1 ± 178.0	0.433
CK-MB AUC (μg h/L)	5629 ± 2625	4720 ± 3342	0.676
Troponin T AUC (μg h/L)	610 ± 219	165 ± 98	0.033
Angiographic characteristics			
Ischemic time	6 h 50 min ± 4 h 28 min	3 h 12 min ± 1 h 10 min	0.244
LAD related infarction (%)	3 (100)	3 (100)	
Multivessel disease (%)	2 (67)	0	0.083
TIMI 0 flow in culprit artery before intervention (%)	3 (100)	3 (100)	
TIMI 3 flow in culprit artery after intervention (%)	3 (100)	3 (100)	
Treatment related characteristics			
Thrombosuction (%)	2 (67)	2 (67)	
Number of stents	1	1	
Stent length (mm)	19.7 ± 2.9	17.0 ± 1.7	0.242
IABP (%)	0	1 (33)	0.273
Reopro (%)	2 (67)	0	0.083
Echocardiographic parameters			
LVEF at baseline	27.5 ± 3.5	44.6 ± 7.4	0.061

LVEF was measured immediately after primary PCI and in the Impella supported patients before Impella implantation

AUC Area under the curve, *LAD* left descending artery, *TIMI* thrombolysis in myocardial infarction, *IABP* intra aortic balloon pump, *LVEF* left ventricular ejection fraction

PVD from 1.6 ± 0.1 to 1.9 ± 0.2 mm/mm^2 ($P < 0.05$) in the Impella group after 48 h of assisted circulation, in comparison to the controls where the PVD remained respectively 1.6 ± 0.2 and 1.6 ± 0.3 mm/mm^2 during the same time course. The mean PVD value of the healthy controls was 1.5 ± 0.2 mm/mm^2.

Hemodynamic and echocardiographic data

In the Impella group, LVEF improved from 28 ± 3% at baseline immediately after PCI to 38 ± 3% ($P < 0.05$) after 3 days (after Impella removal), whereas in the control group no significant improvement was observed. LVEF changed from 45 ± 4 to 37 ± 7% (NS). Thus, the improvement in MC in the Impella group paralleled the functional improvement of LV function.

Discussion

This is the first study describing a positive relationship between effective circulatory support and improvement in sublingual MC, paralleling LV function improvement after STEMI. Our data show that sublingual microcirculatory flow is closely related to LV function improvement. It would support the hypothesis that LV unloading and circulatory support may improve LV function. This phenomenon was demonstrated in STEMI patients with percutaneous LVAD support after PCI [20]. Perhaps SDF imaging of the sublingual microvascular bed may in a way mirror the condition of the myocardium among other parameters and it monitored the effect of adequate circulation and tissue perfusion.

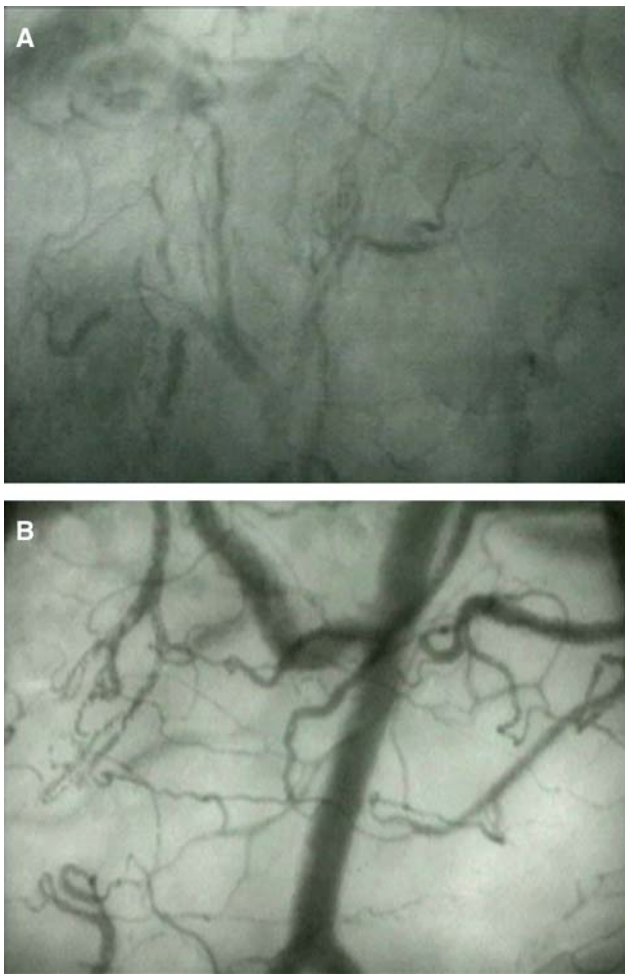

Fig. 1 **a** Microvascular network of a patient from the Impella group at baseline (i.e. after PCI, before initiation of support). **b** MC of a patient from the Impella group after 48 h of assisted circulation

An intact and adequate functioning microvascular network is essential for efficient tissue oxygenation, and consequently, normal end-organ functioning. In our case this also may have led to improved myocardial oxygenation and LVEF. As expected, the worse clinical status of the Impella group was reflected by a more impaired microcirculatory system. The observed microcirculatory dysfunction in STEMI patients may be due to reduced microcirculatory flow, despite seemingly sufficient circulation, especially in the non-support group. Normal MC depending on both the functional capillary density (reflected by PVD) and flow velocity/quality (reflected by MFI) as observed in healthy controls was only achieved in STEMI patients when treated with Impella LP2.5 support. The functional capillary density in both groups was at least at the level of healthy controls, though in the Impella group even above values of healthy controls. The latter may reflect recruitment of microcirculatory vessels in the Impella group. Moreover, the quality of microcirculatory flow (MFI) only in the Impella group reached values of healthy controls.

In other words, our STEMI patients receiving Impella LP2.5 support experienced microcirculatory benefit. In contrast, STEMI patients without support seemed hemodynamically more stable and had better microcirculatory conditions initially. However, in these patients MC did not improve in the first few days, which may reflect sustained microcirculatory distress. Their MC recovered over time but never reached the normal level of healthy persons during the observation period of 72 h. We may assume that despite steady recovery, STEMI patients without circulatory support and impaired MC are exposed to an increased risk of organ failure due to a priori suboptimal tissue perfusion. It has been reported that microvascular deterioration in septic patients, mainly expressed as decreased vascular density, is associated with development of multiorgan failure (MOF) [25, 26]. Besides microvascular hypodensity, several mechanisms such as endothelial cell dysfunction, altered vasomotor tone, reduction of red blood cell deformability and leukocytes adhesions to endothelial walls have a contributing role in progressive organ dysfunction [27, 28]. Furthermore, microcirculatory distress appears to be an independent predictive factor for the clinical outcome of patients in septic shock, and it has been reported that it is of crucial importance that re-establishment of the MC occurs within 24 h [28].

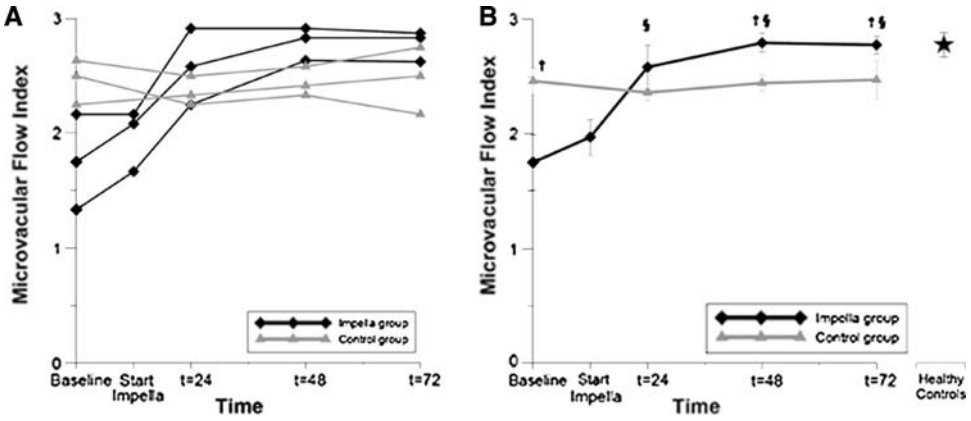

Fig. 2 Microvascular flow index scores for individual patients (**a**) and for the Impella group and non-support group (**b**). Time points depicted are baseline, immediate after start of Impella support, at 24, 48 h of support and at 72 h after removal of the Impella device. *Asterisk* in **b** denotes the mean MFI observed in healthy controls. *Dagger* significant difference ($P < 0.05$) between Impella group and control group. *Section symbol* significant difference ($P < 0.05$) of value compared to baseline within Impella group

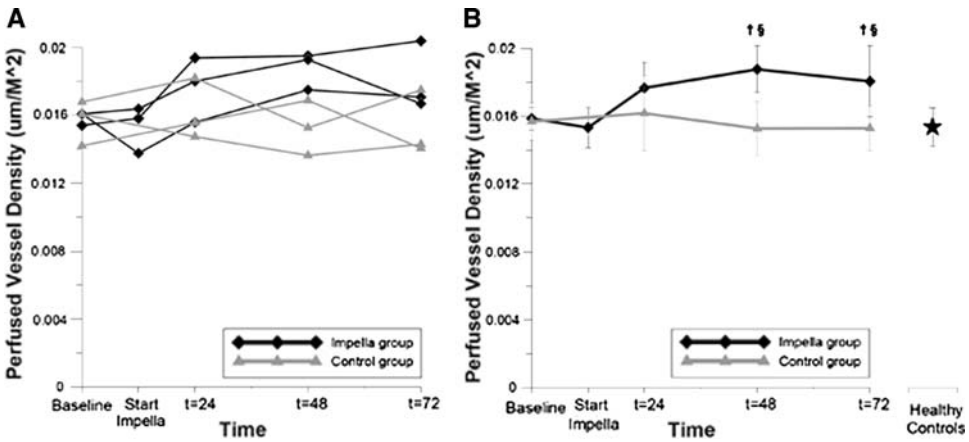

Fig. 3 Perfused vessel densities (estimate of functional capillary density) for individual patients (**a**) and for the Impella group and non-support group (**b**). A*sterisk* in **b** denotes the mean PVD observed in healthy controls. *Dagger* significant difference ($P < 0.05$) between Impella group and control group. *Section symbol* Significant difference ($P < 0.05$) of value compared to baseline within Impella group

Remarkably, our study showed that restoration of the microvascular system was already observed after 24 h of circulatory support in hemodynamically compromised patients, simultaneous to the correction of systemic hemodynamics through the Impella LP2.5 assist device. Moreover, not only did an increase in the microcirculatory flow occur, but also this effect remained up to 72 h of support and was even persistent after removal of the Impella LP2.5. Another point of interest was the observation that the appearance and rating of the MC among normal healthy persons showed a very acceptable uniformity. Therefore, the sublingually obtained MC observations in healthy persons could be used as the normalized standard indeed.

Limitations

Our study has several limitations. First of all, there are limitations to the method used to assess MC. One may question whether the sublingual area is the representative site to monitor MC in general or in specific organs such as myocardial and renal tissue. It has been shown that sublingual MC alterations in patients with severe heart failure and sepsis were adequately related to outcome [28, 29]. Our study substantiates this observation in a different population. Second, acquisition and analysis of the SDF images are operator dependent. Despite a validating scoring system, the selection and quality of the images determine the quality of outcome. An important point of caution with the SDF imaging is the pressure-induced microvascular changes by application of the SDF microscope on tissue surfaces. Also the number of patients studied is small. In the recently initiated IMPRESS in STEMI trial comparing IABP versus Impella LP2.5 in pre-shock STEMI patients, MC assessment by means of SDF and its relationship with LV recovery will be one of the secondary endpoints.

Conclusion

Microcirculation assessed by SDF improved in STEMI patients treated with the Impella LP2.5 to levels observed in healthy persons and remained suboptimal after 72 h in

patients without support. Sublingual SDF to assess MC may serve as a monitor of effective myocardial recovery after PCI and optimization of organ perfusion.

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References

1. Schömig A, Ndrepepa G, Kastrati A (2006) Late myocardial salvage: time to recognize its reality in the reperfusion therapy of acute myocardial infarction. Eur Heart J 27(16):1900–1907
2. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP (2004) ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol 44(3):1–211
3. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H (1993) A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 328(10):680–684
4. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH (1999) Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 341(9):625–634
5. Boden WE, Eagle K, Granger CB (2007) Reperfusion strategies in acute ST-segment elevation myocardial infarction: a comprehensive review of contemporary management options. J Am Coll Cardiol 50(10):917–929
6. Sjauw KD, Engstrom AE, Henriques JP (2007) Percutaneous mechanical cardiac assist in myocardial infarction. Where are we now, where are we going? Acute Card Care 9(4):1–9
7. Henriques JP, de Mol BA (2008) New percutaneous mechanical left ventricular support for acute myocardial infarction. The AMC MACH program. Nat Clin Pract Cardiovasc Med 5(2):62–63
8. Garatti A, Russo C, Lanfranconi M, Colombo T, Bruschi G, Trunfio S, Milazzo F, Catena E, Colombo P, Maria F, Vitali E (2007) Mechanical circulatory support for cardiogenic shock complicating acute myocardial infarction: an experimental and clinical review. ASAIO J 53(3):278–287
9. Minden HH, Lehmann H, Meyhöfer J, Butter C (2006) Transradial unprotected left main stenting supported by percutaneous Impella Recover LP 2.5 assist device. Clin Res Cardiol 95(5):301–306
10. Wettstein R, Erni D, Intaglietta M, Tsai AG (2006) Rapid restoration of microcirculatory blood flow with hyperviscous and hyperoncotic solutions lowers the transfusion trigger in resuscitation from hemorrhagic shock. Shock 25(6):641–646
11. Bateman RM, Walley KR (2005) Microvascular resuscitation as a therapeutic goal in severe sepsis. Crit Care 9 Suppl 4:S27–S32
12. Gori T, Di Stolfo G, Sicuro S, Dragoni S, Parker JD, Forconi S (2006) The effect of ischemia and reperfusion on microvascular function: a human in vivo comparative study with conduit arteries. Clin Hemorheol Microcirc 35(1–2):169–173
13. De Backer D, Creteur J, Dubois MH, Sakr Y, Vincent JL (2004) Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 147(1):91–99
14. Chierego M, Verdant C, De Backer D (2006) Microcirculatory alterations in critically ill patients. Minerva Anestesiol 72(4):199–205
15. Erol-Yilmaz A, Atasever B, Mathura K, Lindeboom J, Wilde A, Ince C, Tukkie R (2007) Cardiac resynchronization improves microcirculation. J Card Fail 13(2):95–99
16. Jung C, Ferrari M, Rödiger C, Fritzenwanger M, Figulla HR (2008) Combined Impella and intra-aortic balloon pump support to improve macro- and microcirculation: a clinical case. Clin Res Cardiol 97(11):849–850
17. Goedhart PT, Khalilzada M, Bezemer R, Merza J, Ince C (2007) Sidestream Dark Field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. Opt Express 15(23):15507–15516
18. Ince C (2005) The microcirculation is the motor of sepsis. Crit Care 9 Suppl 4:S13–S19
19. Almac E, Siegemund M, Demirci C, Ince C (2006) Microcirculatory recruitment maneuvers correct tissue CO_2 abnormalities in sepsis. Minerva Anestesiol 72(6):507–519
20. Sjauw KD, Remmelink M, Baan J Jr, Lam KY, Engström AE, van der Schaaf RJ, Vis MM, Koch KT, van Straalen JP, Tijssen JGP, de Mol BAJM, de Winter RJ, Piek JJ, Henriques JPS (2008) Left ventricular unloading in acute STEMI patients is safe and feasible and provides acute and sustained left ventricular recovery. J Am Coll Cardiol 51(10):1044–1046
21. Henriques JP, de Mol BA (2008) New percutaneous mechanical left ventricular support for acute myocardial infarction. The AMC MACH program. Nat Clin Pract Cardiovasc Med 5(2):62–63
22. Henriques JP, Remmelink M, Baan J Jr, van der Schaaf RJ, Vis MM, Koch KT, Scholten EW, de Mol BA, Tijssen JG, Piek JJ, de Winter RJ (2006) Safety and feasibility of elective high-risk percutaneous coronary intervention procedures with left ventricular support of the Impella Recover LP 2.5. Am J Cardiol 97(7):990–992
23. De Backer D, Hollenberg S, Boerma C, Goedhart P, Büchele G, Ospina-Tascon G, Dobbe I, Ince C (2007) How to evaluate the microcirculation: report of a round table conference. Crit Care 11(5):R101
24. Boerma EC, Mathura KR, van der Voort PH, Spronk PE, Ince C (2005) Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. Crit Care 9(6):R601–R606
25. Vincent JL, De Backer D (2005) Microvascular dysfunction as a cause of organ dysfunction in severe sepsis. Crit Care 9 Suppl 4:S9–S12
26. Doerschug KC, Delsing AS, Schmidt GA, Haynes WG (2007) Impairments in microvascular reactivity are related to organ failure in human sepsis. Am J Physiol Heart Circ Physiol 293(2):H1065–H1071

27. Trzeciak S, Delliner RP, Parrillo JE, Guglielmi M, Bajaj J, Abate NL, Arnold RC, Colilla S, Zanotti S, Hollenberg SM (2007) Microcirculatory alterations in Resuscitation and Shock investigators. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. Ann Emerg Med 49(1):88–98, 98.e1-e2
28. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 166(1):98–104
29. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL (2004) Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 32(9):1825–1831